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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/579,784	05/26/2000	Christopher L. Baszczynski	5718-23B	9894

29122 7590 03/19/2004

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EXAMINER	
KRUSE, DAVID H	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/579,784	BASZCZYNSKI ET AL.	
	Examiner	Art Unit	
	David H Kruse	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/22/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response, arguments and amendment, filed 19 December 2003 has been entered. As agreed upon in the Interview of 30 January 2004, a summary of which having been mailed 9 February 2004, the finality of the Office action mailed 23 September 2003 is herein withdrawn, and Applicant's arguments filed 19 December 2003 are addressed herein.

2. Those rejections not specifically addressed in this Office action are withdrawn in view of Applicant's amendments to the claims.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

4. The specification is objected to because the incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication on page 11, lines 29-30 and page 32, lines17-20 is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

Priority

5. Applicant's claim of domestic priority under 35 U.S.C. § 119(e) to Provisional Application 60/065,628, filed 18 November 1997 is acknowledged. However, this provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. § 112 for claims 1-29 of this application. Applicant's claim of domestic priority under 35 U.S.C. § 119(e) to Provisional Application 60/098,235, filed 28 August 1998 does provide adequate support under 35 U.S.C. § 112 for claims 1-29 of this application, hence this date has been used for the purposes of applying the prior art.

Claim Rejections - 35 USC § 112

6. Claims 3-5, 8, 18, 21 and 22 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At claim 3, line 2, the use of the indefinite article in the phrase "a coding region" renders the claim indefinite because it is unclear what the metes and bounds of this limitation are. See also claim 18.

At claim 4, line 2, "comprises" renders the claim indefinite because the nucleotide sequence of interest would encode a selectable marker and not comprise a selectable marker, as the nucleotide sequence itself is not a selectable marker. See also claim 21.

At claim 5, line 2, "modifies" renders the claim indefinite because it is unclear how the nucleotide sequence of interest modifies herbicide resistance, -- encodes a protein that has -- would obviate this rejection. See also claim 22.

At claim 8, line 2, "a region of the promoter critical for transcription of" is indefinite because it is unclear what the metes and bounds of "critical" are.

7. Claims 1-10, 13-24 and 27-29 remain rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is repeated for the reasons of record in the Office action mailed 23 September 2003. Applicant's arguments filed 19 December 2003 have been fully considered but are not found to be persuasive.

Applicant's clarification of what independent claims 1 and 16 encompass on page 9, 5th paragraph of the Remarks is noted, and is taken under consideration by the Examiner. Those arguments put forth by Applicant as directed to lack of written description because of the issue of indefiniteness of the structure of the chimeric oligonucleotide at claims 1 and 16 are now moot in view of the amendments to the claims.

Applicant argues that ample structure and function is shared among members of the genus to demonstrate possession of the recited chimeric oligonucleotide (page 10, lines 2-5 of the Remarks). This argument is not found to be persuasive because the chimeric oligonucleotides encompassed by the claimed method are only described by general structure, that being capable of recognizing and implementing a nucleotide conversion in a nucleotide sequence of interest that has been transformed into a plant

(see claim 1). As such, Applicant has only described EPSPS and AHAS encoding transgenes of interest and chimeric oligonucleotides that introduce codon changes to produce herbicide resistant enzymes encoded by modified nucleotide sequences of interest. The instant claims encompass any nucleotide sequence of interest regardless of function and as such Applicant has not provided adequate written description of the genus of chimeric oligonucleotides beyond a generic description.

Applicants argue that they have provided in detail the specific common attributes shared among the members of the genus including: 1) the spatial relationship of the DNA and RNA blocks; 2) the structure of the RNA blocks shared by members of the genus (i.e., homology with the nucleic acid molecule comprising the nucleotide sequence of interest); 3) the common structure of the DNA blocks shared by members of the genus; and 4) the common function of the recited chimeric oligonucleotides (page 10, lines 5-10 of the Remarks). This argument is not found to be persuasive because the chimeric oligonucleotides required to practice the claimed method are only described in general structural and functional terms, which do not describe the specific structure of the genus of chimeric oligonucleotides that are capable of recognizing and implementing a nucleotide conversion in a nucleotide sequence of interest as broadly claimed.

See also, MPEP § 2163 which states that the claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its

function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

8. Claims 1-8, 13-22 and 27-29 remain rejected and claims 9-12 and 23-26 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is repeated for the reasons of record in the Office action mailed 23 September 2003. Applicant's arguments filed 19 December 2003 have been fully considered but are not found to be persuasive.

Claims 11, 12, 25 and 26 are rejected as not enabled because the specification teaches that the specific chimeric oligonucleotides encompassed by the instant claims are designed to introduce codon changes into a maize EPSPS or a maize AHAS encoding nucleotide sequence to produce herbicide resistance and are not taught as being capable of recognizing and implementing a nucleotide conversion to inactivate a nucleotide sequence of interest as required by the claimed methods (see the description of the figures on pages 4-6 of the specification).

Applicants arguments on page 12, item I, are now moot in view of Applicants' amendments to claims 1 and 16.

Applicants argue that the art is replete with known alterations including recessive mutations, dominate mutations, stop mutations and frame shift alterations that inactivate a variety of characterized nucleotide sequences and that accordingly, one of skill in the art could readily identify an appropriate alteration that would inactivate a nucleotide sequence of interest. Applicants also argue that alterations in various sequences of interest that are not involved in herbicide resistance are also are known in the art, for example, sequences that play roles in various metabolic pathways, developmental pathways, etc, have been characterized (page 12, item II of the Remarks). These arguments are not found to be persuasive because the scope of the claimed method involves design and use of a myriad of chimeric oligonucleotides to inactivate a nucleotide of sequence of interest introduced into a plant cell or plant. As such the design and use of such chimeric oligonucleotides was not a predictable art at the time of Applicant's invention as broadly claimed.

Applicants argue that the instant specification provides data demonstrating two independent target sequences within the endogenous maize AHAS sequence were modified in a site-specific fashion thereby conferring resistance to either imidazolinone or sulfonylurea herbicides and that the specification teaches a conversion frequency of 100 fold greater than that arising from spontaneous mutation, that the conversion frequency is high enough to allow for the successful identification and selection of a plant cell having the desired alteration (page 13, 4th and 5th paragraphs of the Remarks). These arguments are not found to be persuasive for the reasons given supra. In addition, Applicant teaches that in the case of targeted changes in the coding

sequence of AHAS165 and PAT/GFP, most mutations were due to substitution of different nucleotides (page 29, lines 5-6 of the specification), and thus were not predicted.

Applicants argue that they have successfully identified accessible target sites in two independent PAT/GFP transgenes having distinct and independent chromosomal positions and that two different positions in the AHAS gene were also successfully targeted, that the specification provides specific guidance for target sites in EPSPS, and moreover, provides general strategies for determining appropriate target sites in other genes (page 14, 3rd paragraph of the Remarks). This argument is not found to be persuasive for the reasons given supra.

In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

In the instant case, Applicant has provided limited guidance on how to use the claimed methods within the full scope of the claim. Applicant provides no examples of inactivating a nucleotide sequence of interest comprising introducing at least one chimeric oligonucleotide capable of recognizing and implementing a nucleotide conversion in said nucleic acid molecule. Beetham *et al* (1999 Proc. Natl. Acad.

96:8774-8778) found that the modified base in the Pro-196 codon was always found to be one nucleotide 5' of the mismatch nucleotide (page 8776, right column 3rd paragraph), and Kochevenko *et al* (2003 Plant Physiology 132:174-184) found that depending upon the target site, multiple codon changes would occur that were not predicted by use of the chimeric oligonucleotide (see Table 1 on page 179). Hence, the instant art does not support an argument of routine experimentation for use of the a chimeric oligonucleotide to activate a nucleotide sequence of interest introduced into a genome of a plant cell or plant as broadly claimed. The art teaches that the predicted change using chimeric oligonucleotides comprising a nucleotide mismatch has consistence produced unexpected changes in the gene sequence (see Hohn and Puchta 1999, Proc. Natl. Acad. Sci. USA 96: 8321-8323, especially page 8322). The art teaches, as directed to the nature of the invention, that the efficiency of the gene correction process, using chimeric oligonucleotides, may be influenced by the differential recognition of mismatches by repair enzymes and possible sequence context effects (Anderson *et al* 2002, J. Mol. Med. 80: 770-781, page 770, right column). Anderson *et al* also teach that RDO-mediated gene correction (using chimeric oligonucleotides as taught by Applicant) has been achieved in plants and that introduction of point mutations in specific plant genes leading to herbicide resistance has been accomplished *in vivo* in both tobacco and maize plants but that surprisingly, mixed base sequences other than the predicted nucleotide conversion have been observed, suggesting a plant-specific repair mechanism different from the high-fidelity repair observed in the mammalian system and that this "unspecificity" has later been

confirmed in an *in vitro* study using a tobacco cell-free extract. Anderson *et al* teach that the correction efficiencies of mutated bases obtained are in most cases still inadequate for clinical use, and a considerable variation (0.003-60%) in the degree of correction has been reported both *in vitro* and *in vivo* and that part of this can be ascribed to differential recombination and repair potential in the various cell types used as well as different donor samples exhibiting differences in the amenability towards gene correction. The variable observations reflect the fact that the mechanisms underlying the RDO-mediated gene conversion are not fully understood (page 772, right column). Anderson *et al* also teach that a better understanding of the mechanism underlying the activation of the endogenous repair pathways and the protein factors involved should eventually permit manipulation of the individual steps of the gene correction (paragraph spanning pages 778-779). Therefore, given the limited guidance by Applicant, the unpredictability of the claimed invention, and the nature of the invention, the Examiner maintains that the instant invention is not enabled within the full scope of the claims.

Claim Rejections - 35 USC § 103

9. Claims 1-10, 13-24 and 27-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Kmiec (U.S. Patent 5,731,181, filed 17 June 1996) in view of Dale *et al* (1991 Proc. Natl. Acad. Sci. USA 88:10558-10562).

Kmiec teaches a method of introducing an alteration in a target sequence of the genome of a plant cell comprising providing an oligonucleobase (syn. chimeric oligonucleotide as used by Applicant) at claims 30-32. Kmiec also teaches that said

method can be used to introduce stop codons or frame shift mutations to make knock-outs to produce transgenic plants that lack a functional copy of a specific gene (see column 6, lines 59-64).

Kmiec does not teach introducing a stop codon or frame shift mutation into a selectable marker such as herbicide resistant 5-enol pyruvateshikimate-3-phosphate synthase (EPSPS) or acetohydroxy acid synthase (AHAS), or into a promoter region *per se*.

Dale *et al* teach that it was desirable for one of ordinary skill in the art at the time of Applicant's invention to remove nucleic acid molecules encoding selection markers from transgenic plants after a desirable transgene had been introduced (see page 10558 and page 10561).

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's invention to modify the teachings of Kmiec given the motivation and teachings of Dale *et al*, to introduce a stop codon or frame shift mutation into the coding sequence or promoter region of a selection marker transgene. Use of the specific herbicide resistant EPSPS and AHAS selection markers to select for transformed monocot and dicot plants, including the monocot maize, were well know and widely used in the art at the time of Applicant's invention and would not in themselves lead to the teaching of unexpected results (see page 11, lines 29-30 and page 22, line 20 of the specification). Given the teachings of Kmiec, one of ordinary skill in the art at the time of Applicant's invention would have had a reasonable expectation of success given the motivation of Dale *et al*.

Conclusion

10. This Office action is non-final.

11. No claims are allowed.

12. Claims 10, 11, 25 and 26 are free of the prior art which neither teaches nor fairly suggests the specific chimeric oligonucleotides or use thereof.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (571) 272-0799. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy Nelson can be reached at (571) 272-0804. The fax telephone number for this Group is (703) 872-9306 Before Final or (703) 872-9307 After Final.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

AV 1638

David H. Kruse, Ph.D.
10 March 2004

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